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# *Periarteritis Nodosa & Related Disorders of Blood Vessels*

ROBERT P. McCOMBS

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## Disease-a-Month

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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# *Periarteritis Nodosa & Related Disorders of Blood Vessels*

ROBERT P. McCOMBS

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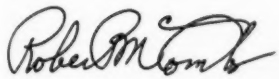

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PATHOLOGIC DESCRIPTIONS of multiple gross nodular or aneurysmal lesions of visceral arteries were recorded as long as 200 years ago, but it was not until 1866 that a clinical-pathologic correlation was made by Kussmaul and Maier (1) and the term "periarteritis nodosa" was coined. The first case described was that of a young man with a protean clinical syndrome characterized by fever, weight loss, weakness, muscle tenderness, subcutaneous nodules, paresthesias and, later, widespread paralysis and colicky abdominal pain. Although the course of the disease was remittent, death occurred 4 months after its onset. On postmortem study, visible nodular, aneurysmal lesions of small arteries were noted, especially in the muscles. Microscopic study indicated the existence of inflammatory changes in the walls of the vessels.

Since the original description, approximately 1,000 cases of periarteritis nodosa have been reported, mostly in small series or in single case reports. In some of these cases, however, other forms of vasculitis may have been incorrectly diagnosed as periarteritis nodosa.

A number of variants of the classic syndrome of periarteritis nodosa have been described in recent years; and in many cases, new names have been introduced, thus creating a confusion of nomenclature.

Some authorities consider the term "periarteritis nodosa" to be a misnomer because the primary lesion is in the vessel walls; they prefer the term "polyarteritis nodosa" because all three coats of the vessels are involved. Localized forms of periarteritis nodosa are occasionally noted in the skin or in a single viscus. A respiratory-renal type of periarteritis nodosa has been described, characterized by granulomatous changes in the upper respiratory passages and lungs, plus necrotizing vasculitis, usually involving the spleen and kidney. This type has been given several names: Wegener's granulomatosis, allergic granulomatous angiitis, allergic granulomatosis (2) and pathergic granulomatosis. A form of necrotizing vasculitis similar to periarteritis nodosa was observed in serum sickness and in reactions caused by sulfonamides and other drugs. Since these reactions involve only small blood vessels, the term "microscopic periarteritis nodosa" has been proposed. Zeek (3) believed that these reactions could and should be delineated from periarteritis nodosa; and, since most cases seemed to be related to drug reactions, she used the term "hypersensitivity angiitis." In describing additional variations of this syndrome, we (4) have preferred the term "allergic vasculitis" and have stressed the differentiation from classic periarteritis nodosa because of differences in treatment and prognosis.

Vasculitis is regularly found in a variety of diseases, such as trichinosis, systemic lupus erythematosus, dermatomyositis, rheumatic fever and advanced hypertension, all of which may be confused at times with periarteritis nodosa. In temporal arteritis, the vasculitis is fairly well localized. Vasculitis also occurs in vessels exposed to infection, trauma, thrombosis or embolus. It is seen adjacent to tumors and eruptive xanthomatoses. Thus, it is apparent that inflammation of the walls of blood vessels occurs in response to many different stimuli and that the finding of vasculitis does not in itself indicate the nature of the pathophysiologic process that produced it.

This welter of nomenclature demands that there be some organization and simplification. As a step in this direction, the classification shown in the accompanying table is suggested.

SYNDROMES ASSOCIATED WITH VASCULITIS

I. *Generalized vasculitis*

- A. Periarteritis nodosa
- B. Systemic allergic vasculitis
  1. Serum sickness
  2. Drug hypersensitivity
  3. Systemic hypersensitivity reactions to infection
  4. Unknown causes
- C. Vasculitis in other "allergic" diseases
  1. Systemic lupus erythematosus
  2. Dermatomyositis
  3. Rheumatic fever
  4. Acute glomerulonephritis
- D. Accelerated hypertension

II. *Localized vasculitis*

- A. Cutaneous allergic vasculitis
  1. Purpura simplex
  2. Urticaria and angioneurotic edema
  3. Sensitization dermatitis
  4. Erythema nodosum
  5. Nodular vasculitis
  6. Migrating phlebitis
- B. Temporal arteritis
- C. Localized visceral allergic vasculitis
  1. Loeffler's syndrome
  2. Parasitic disease (trichinosis, schistosomiasis)
  3. Appendix, gallbladder, etc.
- D. Miscellaneous types
  1. Trauma
  2. Infection
  3. Thrombosis and embolism
  4. Tumors and xanthomas

## GENERALIZED VASCULITIS

*Periarteritis nodosa.*—We have found it convenient to retain the original concept of periarteritis nodosa and therefore require the following for diagnosis: Clinically, periarteritis nodosa is a severe illness characterized by multiple system involvement, usually with a combination of two or more of the following: peripheral neuritis, gastrointestinal bleeding, renal failure, secondary hypertension, myocarditis, cerebral involvement and allergic manifestations. Pathologically, periarteritis nodosa is char-

acterized by involvement of *medium-sized* arteries and arterioles with diffuse involvement of various organs, including the lungs.

*Systemic allergic vasculitis.*—Serum sickness commonly occurs within 7–10 days after the administration of a therapeutic or prophylactic heterologous serum. Similar reactions are sometimes observed after the administration of some drugs, especially penicillin. Clinically, serum sickness is characterized by the occurrence of fever, arthralgia, urticaria, angioneurotic edema, dermatitis, neuritis and occasionally glomerulitis. The course is usually benign, with recovery within a few weeks, presumably when the antigen has been completely metabolized or neutralized. Pathologic study reveals involvement of *small* blood vessels.

One form of systemic allergic vasculitis resembles serum sickness in many respects but differs in that an etiologic agent is not always apparent immediately. A reaction to infection may be present also. The clinical manifestations are more protean. Renal involvement occurs more frequently and may be serious. Pathologically, the vascular lesions are diffuse and occur predominantly in the small arterioles, capillaries and venules.

Wegener's granulomatosis is probably another variant of systemic allergic vasculitis.

Periarteritis nodosa and the various forms of systemic allergic vasculitis are discussed together below because of their many similarities and important differences (5).

## Periarteritis Nodosa and Systemic Allergic Vasculitis

Incidence.—Classic periarteritis nodosa is a rare disease. It is seen only occasionally in community hospitals; and even in reference centers, it is still a medical curiosity. At the New England Center Hospital we have established the diagnosis only 14 times in 22 years, and in the course of studying over 130,000 patients.

On the other hand, systemic allergic vasculitis in its various forms is a more common disease. During the same period at the New England Center Hospital the diagnosis of systemic allergic vasculitis has been established pathologically in 40 cases and clinically in many more. Most of these diagnoses were made within the past 10 years. The incidence is increasing, partly because (1) we know more about the disease; (2) more biopsies

are performed in obscure cases; and (3) there has been a tremendous increase in the number of sensitizing drugs used in medical practice.

AGE.—Periarteritis nodosa may appear at any age, cases having been reported from shortly after birth to the 8th decade. There seems to be no age factor in allergic vasculitis.

SEX.—Most of the patients with periarteritis nodosa are males, in a ratio of 4 to 1. When periarteritis nodosa is associated with bronchial asthma, however, Rackemann and Green (6) noted a preponderance of females. Seven of the 8 cases in their series and 10 of 19 previously reported in the literature occurred in females. In our series, 11 of 14 cases occurred in females.

In our experience, about 60% of the cases of systemic allergic vasculitis occurred in males.

RACE.—Periarteritis nodosa and systemic allergic vasculitis occur in all races.

ETIOLOGY.—Because of the whitish appearance of the nodular lesions in the muscles, Kussmaul and Maier (1) at first thought that periarteritis nodosa was a parasitic disease. This concept was soon disproved. Virchow reviewed some of the original sections and indicated that he had seen similar lesions in syphilis. The erroneous concept that periarteritis nodosa was due to syphilis prevailed for many years. Many attempts to identify infectious agents have been unsuccessful. In a recent paper reporting an analysis of 111 proved cases of polyarteritis nodosa, Rose (7) stated that there was a high incidence of infections of the upper and lower respiratory tract preceding the onset of the disease. In a number of our cases of systemic allergic vasculitis, infection may have been an initiating factor, possibly through an allergic mechanism. In some cases the treatment of the infection may have played a part.

Current concepts relate periarteritis nodosa and systemic allergic vasculitis to hypersensitivity. Gruber (8) in 1925 produced necrotizing vascular lesions in experimental animals and suggested that hypersensitivity to foreign substances might be involved in periarteritis nodosa. This concept was accepted by other workers in the field (9). Rackemann and Green (6) in 1939 were the first to point out the association of well-recognized allergic manifestations, such as bronchial asthma, allergic rhinitis

and marked eosinophilia with periarteritis nodosa. This association was present in 12% of the cases they culled from the literature. Later, Wilson and Alexander reported, in a more comprehensive study (10), that the incidence of atopy in periarteritis nodosa was over 25%.

Clark and Kaplan (11) were the first to demonstrate vasculitis in human serum sickness. Later, Rich (12) noted generalized, acute, necrotizing vasculitis at autopsy in patients who had received therapeutic serum, sulfonamides, or both. It was assumed that the disease was periarteritis nodosa, although the lesions were noted only microscopically and although the gross nodular lesions previously considered characteristic were not present.

Rich and Gregory (13) noted similar lesions in a case of iodine sensitivity and produced vasculitis in animals by inducing drug hypersensitivity. The sulfonamides, penicillin, iodine and diphenylhydantoin (Dilantin) seem to be the drugs most commonly responsible for the induction of necrotizing vasculitis in human beings; many other compounds may, on occasion, be responsible for allergic reactions of this type. In nearly all cases of vasculitis induced by drugs or serum, only the small blood vessels are involved; and in many instances, the disease is self-limited. These, then, would fit into the category of systemic allergic vasculitis.

Experimentally, it is quite easy to induce serum disease in rabbits, and a variety of necrotizing vascular lesions are demonstrable. Using the technic of tagging the antibody with a fluorescent material. Mellors and Ortega (14) demonstrated a high content of gamma globulin (presumably antibody) in the intravascular lesions of periarteritis nodosa.

It is interesting to speculate that autoantibodies to human blood vessels are formed in some manner and that periarteritis nodosa and allergic vasculitis are due to the resulting antigen-antibody reaction within the vessel walls. It must not be concluded, however, that all authorities agree on the hypothesis that periarteritis nodosa is due to hypersensitivity. While conceding that hypersensitivity angiitis (systemic allergic vasculitis) is due to an allergic mechanism, Zeek and her associates (3) suggested that the vascular changes in periarteritis nodosa were due to hypertension. Necrotizing vascular lesions are found in experimental hypertension and in patients with rapidly advancing hy-

pertension, whether primary or secondary to renal disease. Nevertheless, hypertension is not always present in periarteritis nodosa.

PATHOLOGY.—In classic periarteritis nodosa, the lesions are predominantly in the medium-sized arteries, usually at the bifurcations or in the hilar regions of viscera where smaller vessels originate, although the lesions occasionally may involve small arterioles. Zeek and her co-workers (3) maintain that lesions are not found in the pulmonary circulation unless pulmonary hypertension exists, that bronchial arteries are frequently involved and that the spleen is not affected. The lesions initially reveal fragmentation, degeneration and focal edema of the adventitial collagen. Necrosis then begins in the media and spreads to involve the entire vessel wall. This necrosis is associated with inflammation, polymorphonuclear (often eosinophilic) infiltration, edema, fibrin deposition, destruction of the elastic tissue and the intima, and thrombosis of the affected vessel. An aneurysm may be produced, and an infarction of the tissues supplied by the vessel may occur. The inflammatory lesion may be localized to a small segment of the vessel, or the inflammation may spread distally as well as proximally. Inflammatory nodules may be formed in tissues.

A later stage is characterized by formation of granulomas, proliferation of fibroblasts, round-cell infiltration and, at times, formation of giant cells. Vessels may become recanalized. A healed stage may be detected in which a mass of vascularized fibrous tissue completely replaces a section of vessel wall; the vessel may become so scarred as to be almost unrecognizable (15).

At postmortem, lesions may be found in all stages of development. Every organ, including the central nervous system and peripheral nerves, may be affected. The kidneys are frequently involved; with healing, glomeruli become scarred and functionless. Lesions affecting the intestinal tract may be accompanied by ulceration and hemorrhage. The coronary vessels may be affected and may cause myocardial infarction.

In systemic allergic vasculitis, only arterioles, capillaries and venules are involved. All organs, including the lungs and spleen, are affected. There is no predilection for lesions to occur at the bifurcations of arterioles. The primary lesion seems to be endo-

thelial swelling and proliferation with secondary necrosis, vascular and perivascular inflammation, thrombosis with hemorrhage, edema and fibrin deposition in the interstitial spaces. There may be lesions in all stages; healed lesions are common, especially in treated cases.

CLINICAL MANIFESTATIONS: *General.*—Although the onset of periarteritis nodosa may be insidious, there is, as a rule, fairly rapid progression of the disease. Its systemic nature is usually obvious, with fever, weakness and weight loss being prominent. In some cases, there are no localizing symptoms or signs, and hidden infection is often considered and "treated." It is only when antibacterial therapy fails that the noninfectious causes of fever, especially the collagen group of diseases and lymphomas, are considered. In clear-cut cases of periarteritis nodosa, the diagnosis can usually be made once the disease has been considered.

Fever was present in only 35% of our cases of systemic allergic vasculitis, whereas it was present in 93% of patients with periarteritis nodosa. Seventy-one per cent of the patients with periarteritis nodosa lost weight, while only 24% of those with systemic allergic vasculitis did. In systemic allergic vasculitis, the onset is usually insidious, the course of the disease is milder, and, as will be seen later, the condition is more often self-limited than is true in periarteritis nodosa.

Allergic factors are prominent in these diseases. A background of allergic disease is fairly common in periarteritis nodosa, and the sudden occurrence of intractable bronchial asthma, severe allergic rhinitis or eosinophilia may herald the onset of the disease. These manifestations occur in nearly half of the cases of periarteritis nodosa, but they are quite uncommon in systemic allergic vasculitis. Drug reactions are common and may seem to be the triggering factor. Thus, in any obscure condition, the association of allergy should arouse suspicion of the existence of diffuse vasculitis.

*Rheumatic symptoms.*—Arthralgias and myalgias occur in about half of the cases, both in periarteritis nodosa and systemic allergic vasculitis. Joints of the extremities are usually affected and symptoms may be mild, moderate or severe; multiple joints are usually involved. At times, swelling of joints occurs and disuse atrophy of adjacent muscles is evident.

Myositis and myalgias due to inflammation of muscular arteries are less common. In such cases, the exquisite tenderness of the affected muscles and the profound muscular weakness may suggest dermatomyositis (Fig. 1). The differential diagnosis between

FIG. 1.—Myositis in systemic allergic vasculitis. Muscle biopsy from a man, 47, with past history of asthma, who developed ascites, fever, weight loss, muscle tenderness, sensory loss of the extremities and a petechial rash. There was eosinophilia, and skin biopsy showed an acute inflammatory reaction in the capillaries. The above section shows degeneration and segmentation of the sarcoplasm. The patient recovered after a course of corticosteroid therapy, but maintenance therapy was required.

dermatomyositis and periarteritis nodosa may be difficult during the early stages, the true nature of the disease becoming apparent only as other systems become involved.

*Dermatologic manifestations.*—Purpura, erythematous nodules, diffuse sensitization dermatitis, ulcerations, gangrene or edema are characteristic findings in systemic allergic vasculitis; they occur

less frequently in periarteritis nodosa (Fig. 2). The dermatitis involves the legs usually, but it may appear in any area, especially in the areas exposed to sunlight. The dermatologic manifestations result from the involvement of the small blood vessels in the corium, and the degree of involvement determines the nature of

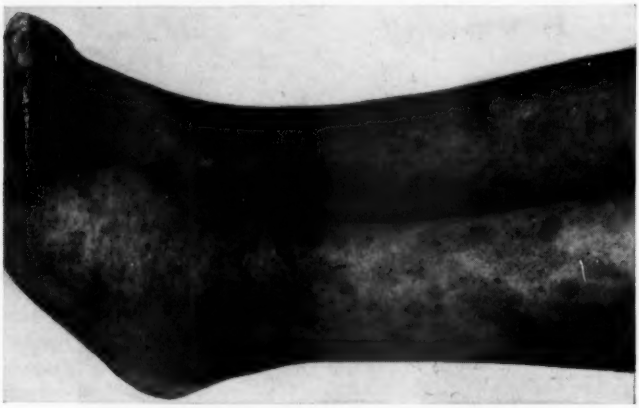

FIG. 2.—Necrosis and purpura of the skin in acute periarteritis nodosa. The symptoms, in this 63-year-old woman, began 6 years previously with arthralgia; the rash was of 2 years' duration. Three months before admission, fever, cough, neuritis and weight loss of 15 pounds occurred. Skin biopsy was inconclusive, but muscle biopsy showed inflammatory obliterative vascular lesions. Death occurred within a few months from renal failure despite corticosteroid therapy. Autopsy revealed fulminating periarteritis nodosa with involvement of multiple organs.

the findings. The edema is caused by the extravasation of serum proteins into subcutaneous spaces; the nodules, by perivascular inflammation; the purpura, by vessel rupture and hemorrhage; and the necrosis and gangrene, by thrombosis. These manifestations may appear alone or in association with one another. In some instances, the dermatologic changes may dominate the clinical picture, and the systemic nature of the disease may be obscured by intense itching or surface pain.

*Peripheral neuropathies.*—Involvement of the nutrient vessels of the peripheral nerves causes degeneration of the nerves, initially producing pain, numbness and tingling, and later producing wrist drop, foot drop, paralysis and muscular atrophy. Major neuropathies are more likely to occur when the larger vessels are involved. Because of the patchy involvement of vessels, a single branch of a nerve may be affected at first, followed by progressive neurologic changes elsewhere. Cranial nerves may be affected, but usually in association with cerebral involvement as well. These disorders will be discussed later.

*Renal manifestations.*—More than any other single factor, the degree of renal involvement determines the prognosis in diffuse vasculitis. The involvement of large vessels produces lumbar pain, gross hematuria, rapidly progressing hypertension and renal failure. When only small blood vessels are involved, glomerulitis results; this condition is characterized by microscopic hematuria, albuminuria, granular casts and red blood cell casts. Careful microscopic examination of a fresh urine specimen aids in the diagnosis. In these cases, renal failure develops gradually and usually progresses despite corticosteroid therapy. When death occurs in systemic allergic vasculitis, it is due to renal failure. Fortunately, renal involvement occurs in less than half of the cases of systemic allergic vasculitis. It is more common in periarteritis nodosa.

*Gastrointestinal manifestations.*—Vessels of the gastrointestinal tract and other abdominal viscera are commonly affected in periarteritis nodosa, causing abdominal pain, acute disturbances of gastrointestinal function and frequently gross or microscopic gastrointestinal bleeding—the result of infarction and ulceration of the intestinal mucosa. The small bowel is probably the most frequent site of involvement. Tenderness, cramps, distention, nausea, vomiting, obstipation or diarrhea may accompany pain and bleeding. These symptoms may lead to surgical exploration of the abdomen, at which time peritonitis and ischemic or gangrenous loops of bowel may be found. The diagnosis of periarteritis nodosa or systemic allergic vasculitis may not be suspected until the pathologist reports necrotizing changes in the blood vessels. The ulcerated lesions in the bowel may be recognized by an astute radiologist.

*Respiratory manifestations.*—Bronchial asthma, often intractable, is a prominent manifestation in allergic patients with periarteritis nodosa; apparently this condition is quite rare in systemic allergic vasculitis.

Pneumonitis is at times a prominent manifestation in a number of noninfectious states thought by many to be allergic in origin (16)—states in which vasculitis may be demonstrated on pathologic examination (allergic vasculitis of the lungs). These include: Löffler's syndrome, allergic (Wegener's) granulomatosis, sarcoidosis, beryllium pneumonitis, hexamethonium pneumonitis and Hamman-Rich syndrome. A similar type of pneumonitis is encountered in periarteritis nodosa and in patients with systemic allergic vasculitis (Fig. 3). This form of pneumonitis is characterized clinically by dyspnea, cough and occasionally hemoptysis. Radiologically, there are diffuse variable pulmonary infiltrates. Dyspnea seems out of proportion to the degree of lung involvement, and pulmonary function tests indicate some degree of alveolocapillary block. Biopsy of the lung reveals necrotizing vascular lesions, interstitial pneumonitis and secondary granulomatous changes.

Klinger and, later, Wegener (17) described an association between granulomatous changes in the upper respiratory tract or lungs and a necrotizing vasculitis, involving mainly the spleen and kidneys. The granulomas in the lung may appear on roentgenograms of the chest as single or multiple circumscribed opacities, suggesting tumor or abscess. We prefer to classify these as cases of systemic allergic vasculitis with pulmonary manifestations, rather than as Wegener's granuloma or allergic granulomatosis, as others have suggested.

*Cardiovascular manifestations.*—Hypertension is a usual sequel to renal damage and may produce cardiac enlargement.

In periarteritis nodosa or in systemic allergic vasculitis, the coronary circulation may become involved: myocardial infarction results when a large vessel is involved; diffuse myocarditis results when only small vessels are affected. The latter causes heart failure which may prove resistant to the usual therapy; but the administration of corticosteroid hormones may quickly cause reversion of a serious situation, just as it may in rheumatic carditis.

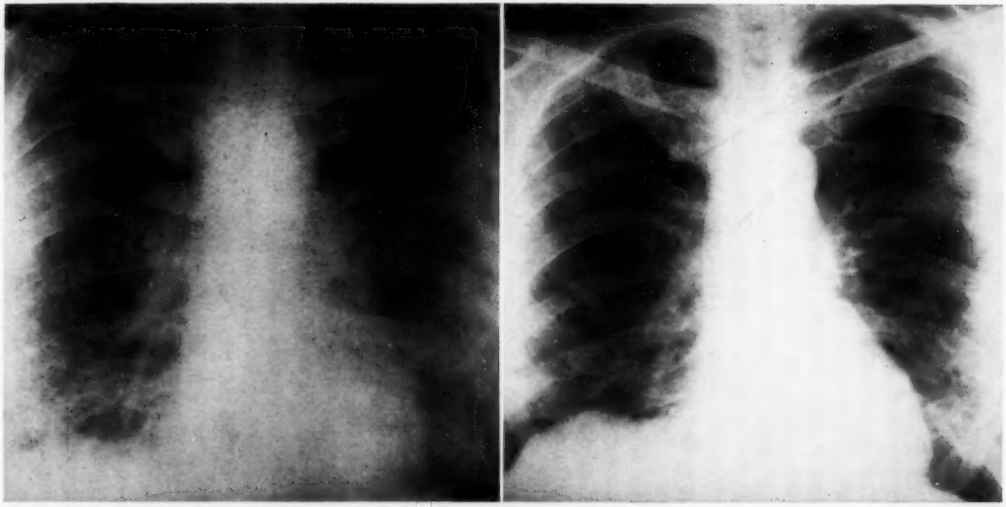

FIG. 3.—Allergic vasculitis of the lungs. *Left,* x-ray showing diffuse pneumonitis in a man, 58, with a moderate degree of dyspnea of only 4 weeks' duration. On physical examination, fine crepitant rales were heard throughout both lung fields. Laboratory studies and retroscalene lymph node biopsy were inconclusive. An open-lung biopsy revealed diffuse interstitial pneumonitis, vasculitis and miliary granulomas; there were no tubercle bacilli. *Right,* x-ray of same patient 4 weeks after institution of corticosteroid therapy. There were only mild fibrotic changes. The entire syndrome recurred a month after corticosteroids were discontinued, only to subside again when therapy was resumed. There was no recurrence 6 months after discontinuance of corticosteroid therapy the second time.

Fibrinous pericarditis or pericardial effusion may occur alone or in conjunction with myocardial involvement.

Any compromise of the peripheral vascular system in the extremities, owing to thrombosis of small vessels, gives rise to claudication, ulceration of skin or gangrene of the digits. Such lesions may have a patchy asymmetrical distribution which may serve as a clue to differentiate this form of vasculitis from other forms of occlusive vascular disease.

*Central nervous system manifestations.*—Thrombosis of major or minor cerebral vessels is fairly common in both periarteritis nodosa and systemic allergic vasculitis. Thrombosis or hemorrhage of the middle cerebral or basilar arteries, with sudden death or visual and cerebellar dysfunctions, has been reported. In some instances, localizing signs are not evident, and the encephalopathic manifestations are due to diffuse involvement of small vessels of the cortex. Symptoms vary from headache and confusion to coma. The spinal fluid reflects the inflammatory process by an increase in protein and cellular elements. The electroencephalogram indicates local or diffuse cerebral damage.

Cranial nerves also may be involved, either alone or in conjunction with other cerebral abnormalities. Bilateral deafness occurs rarely and may be associated with interstitial keratitis (Cogan's syndrome). The central retinal artery may become occluded and induce unilateral blindness. Other retinopathies are evident, particularly in association with hypertension and renal disease.

LABORATORY FINDINGS.—The *white blood count* is usually elevated, and eosinophilia (over 4%) occurs in almost half of the cases of periarteritis nodosa. Leukocytosis and eosinophilia may occur in systemic allergic vasculitis, but in less than one quarter of the cases. Leukopenia is rare.

*Anemia,* when present, is usually associated with uremia, in which bone marrow suppression is a factor. Hemolytic anemia is unusual. The *blood sedimentation rate* is rapid in nearly all cases of periarteritis nodosa and systemic forms of allergic vasculitis during active (inflammatory) stages of the disease. An abnormally high sedimentation rate for which there is no other cause should arouse the suspicion of generalized vasculitis.

*Abnormalities of the serum proteins* are relatively uncommon in periarteritis nodosa, but high globulin values (often considered

to be an expression of rapid antibody formation) are encountered in about 50% of the cases of systemic allergic vasculitis. This lends further credence to the allergic nature of this disorder. The findings in tests for L.E. cells are negative.

The *abnormalities of the urine* which are present both in periarteritis nodosa and systemic allergic vasculitis have already been mentioned. When present, they consist of albuminuria of varying degree, microscopic and occasionally gross hematuria, granular and red blood cell casts and gradually progressing renal failure.

Clinical course.—Periarteritis nodosa is usually a relentlessly progressive disease. Fever, weight loss, arthritis, neuritis, abdominal pain, gastrointestinal bleeding and often bronchial asthma are prominent. Death, from cardiac, cerebral or acute renal failure, may occur in 2 or 3 months after the onset. If the patient survives a year or two, death is usually due to uremia. Remittent and healed forms of periarteritis nodosa have been described (15). One case was observed during several active episodes over a 21-year period (18), during which the disease simulated dermatomyositis and systemic lupus erythematosus.

Systemic allergic vasculitis, on the other hand, tends toward spontaneous remission, especially when the factor which precipitated the reaction can be eliminated, such as a sensitizing drug. In some instances, however, damage to vital organs is so severe during the acute stages that the changes are irreparable even though remission of the active process occurs. This is especially true when there has been renal involvement. In those cases in which the sensitizing factor is unknown, signs of activity of the vasculitis may persist indefinitely, suggesting that the antigen (if such be present) continues to exist in the tissues. Such a state, for example, may exist for many months following injection of long-acting types of penicillin and theoretically may exist in certain viral infections.

Prognosis.—In our series of 14 patients with periarteritis nodosa, 9 died within 2 years of onset. Of those still alive, the longest duration of the disease has been 4 years. In 40 proved cases of systemic allergic vasculitis, 12 patients recovered completely; 18 have residual diseases (renal disease, hypertension, peripheral vascular insufficiency, recurring purpura, pulmonary scarring), and 10 have died (8 of renal failure, 1 of gastrointestinal bleeding and 1 of heart failure). Death occurred within

6 weeks of onset in 1 case, in less than a year in 4 other cases and within 6 years in the remainder. Of the living cases, several have survived more than 4 years from the onset. We believe that in some patients the clinical course has been modified by treatment.

TREATMENT.—Corticosteroid hormones exert a definite suppressive effect on the inflammatory vascular lesions, and unless vital centers have been irreparably damaged, recovery is possible. Fever, arthralgia, purpura, dermatitis, myositis, asthma, pneumonitis, carditis and encephalitis—all may respond within a few days to full doses of corticosteroid hormones. If a response is not evident within 48–72 hours, the dosage of the hormones should be increased. Usually a beneficial effect is observed on doses of 15–20 mg. of prednisone or its equivalent, given every 8 hours; but in seriously ill patients in whom response to therapy has been poor, the dosage may be increased to as much as 25 mg. every 6 or even every 4 hours. Improvement means return of body temperature to normal, improved appetite, loss of pain and subsidence of the visceral manifestations of the disease.

Not all patients are helped with steroid therapy. The renal manifestations of the disease are peculiarly resistant to corticosteroid therapy (although in a few cases we have seen improvement in renal function). Administration of adequate doses of corticosteroids seems warranted, even though it may appear that the treatment is causing renal failure to progress at first. Corticosteroids have a catabolic effect which may present the kidneys with a nitrogen load they are unable to handle. The serum creatinine reflects the true state of renal function better than does the blood urea nitrogen.

Neuritis is likely to persist for several months because of the slow regenerative properties of peripheral nerves or the lack of adequate nourishment of the nerves when nutrient vessels have become thrombosed.

When muscle tissue has been destroyed, recovery is delayed. A physical therapy program is helpful.

Cardiac failure associated with the diffuse myocardiopathy that sometimes occurs in allergic vasculitis responds to corticosteroid therapy when other measures fail. Response may be gradual, and there may be some residual myocardial damage from myocardial fibrosis.

Encephalopathy seems to be one of the most resistant of the manifestations of diffuse vasculitis, in that recovery, once initiated, is likely to be quite slow. Improvement is recognized by a gradual clearing of the mental status and of the abnormalities of spinal fluid and electroencephalogram. A special problem in this regard occurs when psychosis appears during corticosteroid therapy. The problem then becomes one of deciding whether the psychosis is due to the disease or is a complication of the therapy. In the latter situation, it is imperative that the hormone dosage be lowered and discontinued, if possible; in the former, there is a strong indication for increasing the dose, perhaps to unusually high levels. The finding of abnormalities of the central nervous system would aid in the decision to increase dosage; and their absence would suggest that a toxic, rather than an organic, psychosis exists, indicating a need to reduce the dose of corticosteroids.

Pulmonary involvement in generalized vasculitis responds to corticosteroid therapy in a few days. Healing is accompanied by fibrosis, and the residual scarring may be evident radiographically. Slight diffusion defects may be detectable by pulmonary function tests.

## Vasculitis in Other "Allergic" Diseases

There are many similarities between periarteritis nodosa, allergic vasculitis and other diseases in the so-called "collagen" group. The latter are often considered autoimmune or "allergic" diseases, although proof of this hypothesis is lacking. The similarities lead to erroneous diagnoses because there is present in these diseases a vasculitis which may determine some of the manifestations.

Systemic lupus erythematosus.—In their original description of systemic lupus erythematosus, Baehr, Klemperer and Shifrin (19) noted the existence of a diffuse vasculitis similar to that seen in periarteritis nodosa. The concept that the primary disturbance was in the collagen fibers was developed later (20, 21) and is still debated. Other investigators believe that the lesions in small blood vessels are primary and that the fibrinoid degeneration and swelling of collagen are secondary.

The involvement of serous membranes, causing arthritis, pleurisy, pericarditis or peritonitis, may dominate the clinical picture.

The vasculitis may produce dermatitis, purpura, myocarditis, glomerulitis, myositis, neuritis, and encephalopathy, in a manner similar to that described in periarteritis nodosa.

Certain features are said to distinguish systemic lupus erythematosus from the other syndromes in the "collagen" group. There is a typical erythematous eruption of a "butterfly" distribution over the bridge of the nose. Biopsy shows hyperkeratosis, follicular plugging, atrophy and perhaps changes in the collagen tissues; vasculitis may be present also. A peculiar "onionskin" appearance of the arterioles in the spleen and thickening of the basement membrane of glomerular capillaries have been described as characteristic of systemic lupus erythematosus, but these lesions have been found in other diseases as well. Finally, the L.E. or lupus cell test is considered practically diagnostic of this disease. This phenomenon is associated with an autoantibody to nuclear tissue (probably desoxyribonucleic acid). Hemolytic anemia, leukopenia and thrombocytopenia are common in lupus but rare in the other collagen diseases.

In some cases of systemic lupus erythematosus, some of these distinguishing characteristics may be lacking. In some cases of generalized allergic vasculitis, the clinical characteristics may simulate systemic lupus erythematosus closely, but, of course, none of the factors diagnostic of lupus will be present. It is in these borderline cases that mistakes in diagnosis are commonly made.

The corticosteroid hormones are useful in the treatment of systemic lupus erythematosus; and, occasionally, very large doses are required. Chloroquine may be beneficial in mild cases.

Again, renal involvement usually determines the prognosis, although some deaths occur from cardiac or cerebral complications or from the side effects of steroid therapy.

DERMATOMYOSITIS.—There are many similarities among dermatomyositis, systemic lupus erythematosus, periarteritis nodosa and allergic vasculitis. The cause of dermatomyositis is unknown. In about one fourth of the cases, there is an association of this disease with various forms of carcinoma, which suggests the possibility that in some way the tumor functions as an antigen, and the reactions in the skin, muscles and other tissues that characterize the disease represent the effects of the combination of this antigen with an autoantibody.

Pathologically, dermatomyositis is characterized by vasculitis in the skin and muscles, with secondary inflammation, degeneration and replacement of muscle by scar tissue. The skin may show sclerodermatous changes. Vasculitis may involve the heart, the kidneys and the gastrointestinal tract.

Clinically, dermatomyositis is differentiated from the other diseases in this group by the marked muscle involvement and the peculiarities of a rash. When the rash is present, it is often intensely erythematous; but it may have a bluish (heliotrope) tinge, especially about the eyes and in other exposed areas. The face often becomes edematous. The muscle weakness is greatest in the proximal muscles of the shoulders and hips, profoundly affecting motion of the extremities. Any muscle group may be involved. Muscles of the pharynx are sometimes affected, and pneumonitis is a complication.

Most patients improve after the administration of corticosteroids. Large doses may be required. A program of active and passive muscle exercises is necessary for rehabilitation when muscle involvement has been extensive. When a tumor is present, its removal aids in the control of the muscle disease.

RHEUMATIC FEVER.—Generalized vasculitis has long been known to occur in rheumatic fever; the Aschoff body is probably a manifestation of granuloma formation in the region of an affected vessel. It seems clear that attacks of rheumatic fever are initiated by an allergic reaction to certain types of hemolytic streptococci (22). The arthralgias and myocarditis that characterize rheumatic fever are indistinguishable from those seen in systemic allergic vasculitis. Of course, the endocarditis and valvular damage that appear in the later stages of rheumatic fever are *not* seen in systemic allergic vasculitis.

ACUTE GLOMERULONEPHRITIS.—Types 4, 12 and 25 of beta hemolytic streptococcus are apparently nephrotoxic and may induce attacks of acute glomerulonephritis in susceptible persons, presumably through an allergic mechanism. Antibodies to kidney tissue have been demonstrated in glomerulonephritis. The urinary findings in acute and subacute glomerulonephritis are indistinguishable from those in the renal phases of systemic allergic vasculitis and systemic lupus erythematosus. In acute nephritis, heart failure may occur, although minimal changes are found on

pathologic examination. The degree of systemic and myocardial vasculitis present is variable.

### Accelerated (Malignant) Hypertension

The vascular lesions of accelerated hypertension are microscopically similar to those of periarteritis nodosa. Necrotizing vascular lesions and malignant hypertension have been induced in experimental animals by various technics that do not involve hypersensitivity: by the application of clamps or ligatures to the renal arteries; by encasing the kidneys in silk, cotton or cellophane; by combining unilateral nephrectomy with overdosage of desoxycorticosterone acetate or by the administration of large doses of crude pituitary extract. Malignant hypertension may be present, however, without necrotizing vasculitis. Conversely, in some cases of periarteritis nodosa there is no hypertension. Thus, although some pathologists believe that there is an etiologic relationship between the two disorders, it seems more likely that the necrotizing vasculitis of malignant hypertension is a more advanced reaction to pressor substances, which in milder forms of hypertension cause only arteriolar constriction. Because of the nature of the vasculitis in malignant hypertension, it is tempting to speculate that an allergic mechanism of some sort is involved. There is, to date, however, no evidence to substantiate this concept.

## LOCALIZED VASCULITIS

### Cutaneous Allergic Vasculitis

Vasculitis is a common reaction in the skin, and a number of dermatologic entities characteristically show vasculitis on biopsy (23). It is of more than a little interest, however, that in all of these an allergic mechanism is strongly suspected, although not always proved.

Purpura simplex.—Purpura simplex, or vascular purpura, is a typical example of localized allergic vasculitis. Purpura is the only manifestation of the disease, and it may recur in episodic showers for many years without any symptoms between attacks.

Signs of systemic involvement, such as fever and weight loss, are rare. In some cases of recurrent purpura, however, there are abdominal and joint symptoms (Henoch-Schoenlein purpura), or there may be hematuria. These cases may be more properly classified as forms of systemic allergic vasculitis.

URTICARIA AND ANGIONEUROTIC EDEMA.—Particularly in long-standing cases, mild vasculitis involving small blood vessels may

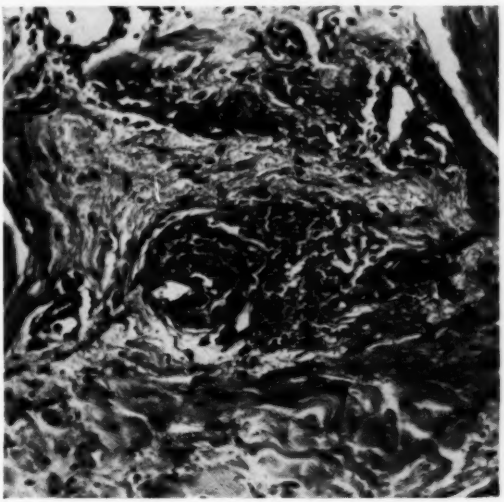

FIG. 4.—Localized allergic vasculitis. Photomicrograph of skin biopsy from a patient with extensive sensitization dermatitis which appeared after application of an ointment containing an antibiotic to an ulcer of the leg. In the center of the section is a small arteriole nearly occluded by swollen endothelial and inflammatory cells. The inflammatory reaction has spread beyond the vessel and also surrounds smaller vessels. There is fibrin deposition in surrounding tissues.

be recognized. Urticaria may be an early symptom of a systemic disease such as systemic lupus erythematosus.

SENSITIZATION DERMATITIS.—Sensitization dermatitis, or "id" reactions, may be localized, as in trichophytid, or more extensive,

as in a generalized sensitization dermatitis due to drug hypersensitivity (Fig. 4). The initial site of sensitization may be obscured by the more extensive generalized eruption. Biopsy of a fresh lesion characteristically shows an acute necrotizing vasculitis, indicating that the sensitizing factor is blood-borne and suggesting that the primary reaction occurs in the wall of the small blood vessels. The erythema, edema, purpura and serous exudate are secondary to the escape of serum and red blood cells from the vascular system into the subcutaneous tissues.

Erythema nodosum.—For a long time, erythema nodosum has been considered to represent an allergic reaction to bacteria or drugs. It is characterized by nodular, inflammatory lesions, usually appearing only on the lower legs. Pulmonary hilar adenopathy may also be present. Biopsy of an early skin lesion shows vasculitis; later there is a kind of granuloma formation.

Nodular vasculitis.—Nodular vasculitis of the skin is probably a variant of erythema nodosum.

Migrating phlebitis.—This condition may be a form of localized allergic vasculitis in which only superficial veins are involved. In some instances, a visceral tumor seems to be the initiating (antigenic) factor. The association of migrating phlebitis with malignant disease is sometimes called "Trousseau's sign."

## Temporal Arteritis

There is general agreement that temporal arteritis is not a localized form of periarteritis nodosa or allergic vasculitis. There are enough distinguishing features of this disorder to warrant its classification as a distinct clinical entity.

Temporal arteritis is not a rare disease. Between 1931 and 1954, 103 cases were seen at the Mayo Clinic, where it was first described by Horton, Magath and Brown (24).

The etiology is unknown. It usually occurs in patients over 55, the average age of onset being about 69 years. It occurs slightly more frequently in women than in men.

Clinically, temporal arteritis is characterized by fever, sweats, weakness, anorexia and headache localized over the branches of the temporal arteries. The vessels are tender and the adjacent

area is swollen and inflamed; later, thrombosis occurs (Fig. 5). That the disease is not confined to the temporal arteries is evidenced by the fact that in some cases the occipital arteries are also swollen and painful and other cranial arteries also may be involved. One or both of the central arteries of the retina may be affected in about half the cases, causing visual disturbances, in-

FIG. 5.—Temporal arteritis. Swollen, tender artery in a 66-year-old man with history of intense head pain of 6 weeks' duration. Biopsy of a branch of the temporal artery showed granulomatous infiltration of the vessel wall typical of temporal arteritis. The entire process subsided following institution of corticosteroid therapy.

cluding blindness. The decrease in blood flow to the retina may be observed ophthalmoscopically. Deafness may occur. In some instances, there are evidences of involvement of major arteries elsewhere in the body.

A moderate to severe anemia is fairly characteristic and apparently is due to "toxic" suppression of bone marrow. The sedimen-

tation rate is, almost always, quite rapid. Rarely there may be hematuria, suggesting involvement of renal vessels. Leukocytosis and abnormalities of serum proteins are usually absent.

The pathology of temporal arteritis is diagnostic, and biopsy is useful. Characteristically, there is considerable thickening of the intima. The walls of the temporal arteries and their branches are involved in a granulomatous reaction with round cell infiltration and occasional giant cells. Numerous capillaries, with swollen endothelial cells, pervade the granulomatous areas. Some eosinophils and polymorphonuclear cells may be present in the inflammatory reaction that surrounds the involved areas. The vessels may be thrombosed.

In most instances, temporal arteritis is a self-limited disease and runs its course in a few months. In some cases, the systemic manifestations antedate the headache that characterizes the disease; in others, blindness may be an early manifestation. Death from the disease occurs in about 12% of the cases.

Treatment of temporal arteritis with full doses of corticosteroid hormones induces dramatic relief of most symptoms quite promptly. The incidence of blindness in this disease has been reduced when treatment has been begun before visual difficulties have developed. Visual loss due to ischemia of the retinal cells is permanent. The dosage of corticosteroid may be reduced gradually as symptoms improve. Because the disease is usually self-limited, it is possible to eliminate the hormone after a month or two. Care must be exercised lest serious osteoporosis be induced or aggravated by corticosteroid therapy in the older age group.

### Localized Visceral Allergic Vasculitis

Loeffler's syndrome is a benign disorder characterized by migrating pneumonitis and eosinophilia. Few pathologic studies of the lungs have been made, but vasculitis involving pulmonary vessels has been described. This condition is one form of allergic pneumonitis; other forms occur in association with systemic allergic vasculitis.

In trichinosis, vasculitis appears adjacent to the parasites during the invasive stage, and systemic allergic reactions are common. In schistosomiasis, an intense vasculitis develops in the portal system

where the parasites are located. Portal hypertension, hypersplenism and ascites result from the scarring that occurs with healing. When ova are released and pass into the systemic circulation, vasculitis develops at the points wherever ova are trapped, usually in the lungs. Vasculitis of the lungs appears in other parasitic diseases.

Pathologists have described "localized periarteritis nodosa" in surgical specimens from the appendix, gallbladder or gastrointestinal tract. There may be an intense local necrotizing vasculitis in these organs without evidence of involvement elsewhere. Probably some local infection or other antigenic factor operating locally is responsible for this type of visceral vasculitis.

It is of interest that all forms of localized allergic vasculitis, whether of skin or viscera, will respond to corticosteroid therapy.

## Miscellaneous Types of Localized Vasculitis

Vasculitis commonly occurs in areas of the body subjected to *trauma.*

Similarly, vascular inflammation participates in the inflammatory reaction of *infected tissue,* and this may be recognized by the finding of micro-organisms in the tissues.

*Thrombosis* and *embolism* may also induce vasculitis. It is unlikely that these types of vasculitis would be confused with periarteritis nodosa or allergic vasculitis. An exception may be the rare disorder, thrombotic thrombocytopenic purpura, in which diffuse vasculitis occurs in areas where clumped platelets cause vascular occlusion.

Vasculitis is sometimes encountered in areas adjacent to *malignant tumors* and *xanthomas.* Because of the frequent occurrence of malignant tumors and the onset of dermatomyositis, migrating phlebitis, peripheral neuritis and arthritis, it has been suspected that tumors may be antigenic and induce autosensitization. On the other hand, some sort of metabolic change may be responsible.

Vasculitis may also occur in association with *eruptive xanthomas.* It seems likely that a metabolic disturbance is responsible for this type of vascular reaction, although its nature is unknown.



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## REFERENCES


1. Kussmaul, A., and Maier, R.: Concerning a hitherto undescribed, unique disease of the arteries (periarteritis nodosa), which is associated with morbus brightii and rapidly progressive generalized muscle paralysis, Deutsches Arch. klin. Med. 1:484, 1866.
2. Churg, J., and Strauss, L.: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa, Am. J. Path. 27:277, 1951.
3. Zeek, P. M.: Periarteritis nodosa and other forms of necrotizing angiitis, New England J. Med. 248:764, 1953.
4. McCombs, R. P., Patterson, J. F., and MacMahon, H. E.: Syndromes associated with "allergic" vasculitis, New England J. Med. 255:251, 1956.
5. McCombs, R. P.: The clinical differentiation of "allergic" vasculitis from periarteritis nodosa, Internat. Arch. Allergy 12:98, 1958.
6. Rackemann, F. M., and Green, J. E.: Periarteritis nodosa and asthma, Tr. A. Am. Physicians 54:112, 1939.
7. Rose, G. A.: Infections and their treatment in the aetiology of polyarteritis nodosa, Proc. Roy. Soc. Med. 49:289, 1956.
8. Gruber, G. B.: Pertaining to periarteritis nodosa, with special consideration of involvement of gallbladder and kidneys, Virchows Arch. path. Anat. 258:441, 1925.
9. Klinge, F.: Protein hypersensitivity of joints (joint anaphylaxis): Experimental, pathological, anatomical study pertaining to the pathogenesis of arthritis, Beitr. path. Anat. 83:185, 1930.
10. Wilson, K. S., and Alexander, H. L.: The relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness, J. Lab. & Clin. Med. 30:195, 1945.
11. Clark, E., and Kaplan, B. I.: Endocardial, arterial, and other mesenchymal alterations associated with serum disease in man, Arch. Path. 24:458, 1937.
12. Rich, A. R.: Role of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy, Bull. Johns Hopkins Hosp. 71:123, 1942.
13. Rich, A. R., and Gregory, J. E.: Experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp. 72:65, 1943.
14. Mellors, R. C., and Ortega, L. G.: Analytical pathology: III. New observations on the pathogenesis of glomerulonephritis, lipid nephrosis, periarteritis nodosa, and secondary amyloidosis in man, Am. J. Path. 32:455, 1956.
15. Arkin, A.: A clinical and pathological study of periarteritis nodosa: A report of five cases, one histologically healed, Am. J. Path. 6:401, 1930.
16. McCombs, R. P.: "Allergic" pneumonitis, Canad. M. A. J. 81:703, 1959.
17. Wegener, F.: Concerning a unique rhinogenous granulomatosis with involvement of the arterial system and the kidneys, Beitr. path. Anat. 102:36, 1939.

18. Kampmeier, R. H., and Shapiro, J. S.: Diffuse and sometimes recurrent course of diffuse arteritis: Observations and report of a patient observed for 21 years, A.M.A. Arch. Int. Med. 92:856, 1953.
19. Baehr, G., Klemperer, P., and Shifrin, A.: A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis), Tr. A. Am. Physicians 50:139, 1935.
20. Baehr, G., and Pollack, A. D.: Diffuse vascular diseases, Mod. Concepts Cardiovas. Dis. 15:12, 1946.
21. Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of disseminated lupus erythematosus, Arch. Path. 32:569, 1941.
22. Swift, H. F., Derick, C. L., and Hitchcock, C. H.: Rheumatic fever as a manifestation of hypersensitiveness (allergy or hyperergy) to streptococci, Tr. A. Am. Physicians 43:192, 1928.
23. Lever, W. F.: *Histopathology of the Skin* (5th ed.; Philadelphia: J. B. Lippincott Company, 1949).
24. Horton, B. T., Magath, T. B., and Brown, G. E.: Arteritis of temporal vessels, Arch. Int. Med. 53:400, 1934.

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